

REMARKS

I. The Office Action

The Office rejected claims 47-141 under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description; and claims 47-112, 117, 118, and 120-141, under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Reconsideration of these rejections is hereby requested. The Applicants acknowledge with thanks the consideration of the previous amendment and withdrawal of other rejections.

II. The Amendments to the Specification and Claims

The specification has been amended to improve a matter of form by reciting, e.g., “Figures 1A and 1B” instead of “Figure 1”. These amendments mirror the amendments made by Examiner’s amendment to the specification in U.S. Patent Application No. 10/102,469, which claims priority to this application.

At the time of the action, claims 47-141 were pending. Claims 71-72 and 74-76 have been cancelled, and claims 55, 59, 79-80, 113-116, 128, and 136 have been amended herein (generally to adopt suggestions of the Patent Office as discussed below in greater detail). No new matter has been added by way of these amendments.

III. The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn.

The Office rejected claims 47-141 under 35 USC §112, first paragraph, alleging inadequate written description. (Action at pages 3-9, paragraph 8.) These rejections are respectfully traversed.

The written description requirement is satisfied when persons of ordinary skill in the art can recognize from the application’s disclosure that the applicants invented what is claimed. *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). As part of the response to the Office action, the Applicants have submitted herewith a Rule 132 declaration from James A. Baum, Ph.D., a scientist whose long experience in the field qualifies him to comment on what one of ordinary skill in the art would have understood from the specification at the time that it was filed in 1989. (See Baum Declaration at paragraph 1.1.)

A. The starting sequences recited in all of the claims are adequately described in the specification.

In paragraph 8, part (a), the Office rejected claims 47, 51, 55, 59, 63, 67, 112, 113, 117, and 119, alleging that “[n]either the instant specification nor the originally filed claims appear to provide support for the concept of the **insecticidal protein coding sequence being from any *Bacillus* species.**” (Office Action, pages 3-6 (emphasis added in bold).) The Office acknowledged that the specification provides support for *Bacillus thuringiensis* crystal proteins, non-plant proteins, and plant proteins, but asserted that the specification fails to provide support for a claim directed to a subset of “non-plant protein” sequences derived from *Bacillus* species (other than *Bacillus thuringiensis*). (Office Action, paragraph (8)(a) at pp. 5-6.) In a related rejection in paragraph 8, part (g), the Office rejected claim 126, alleging that neither the specification nor the originally filed claims support the concept of the starting material for the claimed method being **any insecticidal protein**. The Office asserts that only insecticidal proteins from *Bacillus thuringiensis* are contemplated in the specification. The Applicants respectfully disagree.

1. *The rejection is moot with respect to claims 59 and 67.*

Claims 59 and 67 were amended and now specify *Bacillus thuringiensis*, rendering moot the rejection of these claims.

2. *The intermediate genus of Bacillus coding sequences.*

The application states on page 14 that “it is an object of the present invention to provide a method for preparing synthetic plant genes which express their respective proteins at relatively high levels when compared to wild-type genes,” and states on page 1, first paragraph, that the invention relates to transforming plants to express “a heterologous gene.” The application states at pages 16-17 that the invention has broad applicability to expressing essentially any non-plant genes in plant cells. For example, the first paragraph summarizing the “statement of the invention” says, “The present invention provides a method for preparing *synthetic plant genes* which genes express their protein product at levels significantly higher than the wild-type genes which were commonly employed in plant transformation heretofore. In another aspect, the present invention also provides novel *synthetic plant genes which encode non-plant proteins.*” (Application at p. 16 (emphasis added in italics).) Indeed, the Office acknowledges (at page 6 of the Action) that “the

paragraph spanning pg 16-17 provide support for *Bacillus thuringiensis* crystal proteins, non-plant proteins, and plant proteins.” Thus, clear basis exists for a claim directed to a genus that is broader than *Bacillus* protein or *Bacillus* insecticidal proteins.

The Office also clearly agrees that the application supports the concept of claiming the invention at the subgenus level of insecticidal *Bacillus thuringiensis* protein coding sequences. Thus, the written description rejection in parts (a) and (g) of paragraph 8 appear to involve whether there is adequate written description for intermediate genera that are narrower in scope than “all non-plant protein coding sequences” but broader in scope than *Bacillus thuringiensis* insecticidal protein coding sequences.

Importantly, written description looks not only at the exact words or clauses in a patent application, but at what a person of ordinary skill in the art would have understood the patent application to teach, at the time that it was filed. Dr. Baum provides his analysis of this question in paragraphs 3.2-3.14 of his declaration.

Although the application is heavily focused on *B.t.* insecticidal proteins, the application explicitly states that the purpose of describing the invention in the context of *B.t.* insecticidal proteins was simply for brevity, not to limit the invention: “For brevity and clarity of description, the present invention will be primarily described with respect to the preparation of synthetic plant genes which encode the crystal protein toxin of *Bacillus thuringiensis* (*B.t.*).” (Application at p. 16.) In fact, the application explicitly states, “those skilled in the art will recognize and it should be understood that the present method may be used to prepare synthetic plant genes which encode non-plant proteins other than the crystal protein toxin of *B.t.*” (Application at p. 17.) Thus, a person in the field reading the application would certainly not conclude from the emphasis on *B.t.* insecticidal protein coding sequences that the invention was limited to such protein coding sequences. (See Baum Declaration at paragraph 3.4.)

A researcher who read the application in 1989 would have understood that, within the broader genus of non-plant protein coding sequences, the inventors considered the invention to be particularly applicable to protein coding sequences from the bacterial genus *Bacillus*. (See Baum Declaration at paragraph 2.5.) The claims are directed to removing occurrences of certain adenine and thymine-rich sequences. Specifically, ATTAA sequences and/or Table II polyadenylation signal sequences are rich in adenine and thymine nucleotides.

A variation of the invention focuses on regions of five or more consecutive A or T nucleotides, irrespective of whether they constitute an ATTTA or polyadenylation signal sequence. (See, e.g., application at p. 23 and claim 103.)

The application points to the *Bacillus* genus as being particularly amenable to genetic modification (according to the invention) to enhance protein production in plants. The specification teaches that some *Bacillus* species have genomes among the most rich in adenine and thymine (A+T) bases (see Fischhoff Application at, e.g., page 21, lines 1-15, “For example, some *Bacillus* species have among the most A+T rich genomes”) The reader would have understood that, because the “problem sequences” associated with low protein production are themselves (A+T)-rich, they are apt to occur with greater frequency in an (A+T)-rich genome, such as the (A+T)-rich genome of *Bacillus* bacteria. (See Baum Declaration at paragraphs 3.6 and 3.7.)

The application also discusses the invention with regard to the genus *Bacillus* when characterizing codon usage. “Due to the degeneracy of the genetic code and the limited number of codon choices for any amino acid, most of the “excess” A+T of the structural coding sequences of some *Bacillus* species are found in the third position of the codons. That is, genes of some *Bacillus* species have A or T as the third nucleotide in many codons.” (Application at p. 21; Baum Declaration at paragraph 3.8.)

To summarize, the application as a whole teaches: (i) that the invention was generally applicable to any non-plant protein coding sequence; (ii) that the problem sequences to target for removal were (A+T)-rich sequences; (iii) that *Bacillus* bacteria have among the most (A+T)-rich genomes; and (iv) that the “excess” (A + T) was mostly found in the third position of codons, which were amenable to modification due to the well known degeneracy of the genetic code. From these and related teachings in the application, a person of ordinary skill would have understood from the application that protein coding sequences from the genus *Bacillus* were a preferred class of protein coding sequences for improvement according to the invention. The reader would have understood that the inventors intended to apply the invention to all *Bacillus* proteins as a class, to enhance production in plant cells. (See Baum Declaration at paragraph 3.9.)

3. *The “192 other Bacillus species”*

In the action the Patent Office asserts that there are at least 192 *Bacillus* species other than *B.t.*, and that “[t]here is no support for any of these species in the specification.” (Action at pp. 4-5.) The Patent Office also asserts that the specification “does not provide support for the subset of proteins from other *Bacillus* species.” (Action at p. 6.) These assertions, even if true, do not support a rejection. The claims in question specify the genus *Bacillus* -- none of the claims are specifically directed to one of the other “192 *Bacillus* species” (individually). The failure to specifically mention the other 192 species by name does not support a rejection of the pending genus claims. The Applicants contemplated that the invention was applicable to the *genus* of *Bacillus* bacterial coding sequences, a genus that includes *B.t.* as a representative species.

This invention is a perfect example of a case where identification of the genus (*Bacillus*), and numerous working examples using coding sequences from a species within the genus (*B.t.*), is sufficient to satisfy the written description requirement. M.P.E.P. § 2163.05 recognizes that one species can adequately support a genus. For example, in *In re Herschler*, the C.C.P.A. found that a specification’s disclosure of corticosteroid in DMSO was sufficient to support claims drawn to a method of using a mixture of a “physiologically active steroid” and DMSO. 591 F.2d 693, 697 (C.C.P.A. 1979). The court noted that “use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds.” *Id.* Similarly, the instant claimed method does not depend on the particular coding sequence used as starting material; the invention is in the *method*, including the steps that are performed to modify the starting material.

Moreover, extensive description of the genus *Bacillus*, or other species within the genus, would have been unnecessary in 1989 because bacteriology was already an established field by then. A person of ordinary skill who read the application would already have a knowledge of the field and numerous resources at his or her disposal. For example, the *Eighth* edition of Bergey's Manual of Determinative Bacteriology – a common reference in the field -- already had been published in 1974, some fifteen years earlier. The features common to *Bacillus* (which also distinguish *Bacillus* from other microorganism genera) were known in the field. (See Baum Declaration at paragraph 3.10.) The disclosure required to

satisfy the written description requirement is not fixed, but varies with the nature of the invention and the scientific and technological knowledge in existence as of the filing date of the application. *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) (“[t]he ‘written description’ requirement must be applied in the context of the particular invention *and the state of the knowledge*” (emphasis added)). Forced recitation of known *Bacillus* species would serve no goal of the written description requirement and only add “unnecessary bulk” to the application. See *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1369 (Fed. Cir. 2006) (noting that a requirement for patentees to recite known structures would “neither enforce the quid pro quo between the patentee and the public. . . nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention”).

Moreover, the application *does* teach the common attributes of *Bacillus* species that are relevant to the invention: that they have (A + T)-rich genomes, with most of the excess (A + T) in the third position of codons. The detrimental sequences targeted by the inventors for removal (e.g., ATTAA sequences and listed polyadenylation signal sequences) are (A+T)-rich and are more likely to be present in *Bacillus* coding sequences. These sequences could be identified in any coding sequence, regardless of origin. (See Baum Declaration at paragraph 3.10.)

4. *The application conveys that the invention was considered particularly applicable to pesticidal protein coding sequences and especially applicable to insecticidal protein coding sequences.*

In addition to conveying a preferred (*Bacillus*) and highly preferred (*B.t.*) source for protein coding sequences, the application also conveys preferred and highly preferred classes of proteins for practice of the invention. Insecticidal proteins from *B.t.* clearly are a highly preferred type of encoded protein according to the application, but it is not the only type specifically contemplated by the inventors. For example, on page 17 the specification states that “it should be understood that the present method may be used to prepare synthetic plant genes which encode non-plant proteins other than the crystal protein toxin of *B.t.*” Example 9 (pages 96-98) pertains to potato leaf roll virus (PLRV) coat protein coding sequence recombinantly expressed in plants to produce resistance to a different type of agricultural pest-plant viruses. It also would have been understood that coding sequences for insecticidal proteins were highly preferred by the inventors. Example 7 describes, in

generic terms, a benefit of introducing two different insecticidal proteins into the same plant. (“In other plants, the production of two distinct insect tolerance proteins would provide protection against a wider array of insects.” Application at p. 90.) The specification teaches, “Production of two insecticidal proteins in the same plant with different modes of action would minimize the potential for development of insect resistance to *B.t.* proteins in plants.” (See Baum Declaration at paragraphs 3.11 and 3.12.)

From passages such as these, a reader would have appreciated that the invention was generally applicable to any heterologous protein contemplated for plant expression; that heterologous proteins that provided pest resistance were a preferred class; and that heterologous proteins that provided insect resistance were a highly preferred class contemplated by the inventors. (See Baum Declaration at paragraphs 3.11 and 3.12.) Thus, the rejection of claim 126 was improper, and should be withdrawn.

5. *The Fischhoff application conveys that the invention was considered particularly applicable to insecticidal proteins from *Bacillus*.*

The foregoing analysis demonstrates how the specification would have conveyed to a reader in 1989 that the invention was broadly applicable to any heterologous protein coding sequences contemplated for expression in plants, and was particularly applicable to protein coding sequences from specific *sources* (e.g., *Bacillus* in general and *B.t.* in particular) and protein coding sequences having specific agriculturally beneficial *properties* (e.g., pest resistance in general or insect resistance in particular). These designations as to preferred *source* and preferred *properties* were not described as mutually exclusive. (See Baum Declaration at e.g., paragraph 3.13.) To the contrary, most of the Examples relate to insecticidal proteins from a particular *Bacillus* species (*B.t.*). Accordingly, from reading the Fischhoff application *as a whole*, a reader skilled in the field would have understood that the inventors contemplated practicing the invention with a variety degrees of particularity, including (but not necessarily limited to) the following:

- (i) any plant or non-plant protein coding sequence
- (ii) any non-plant protein coding sequence
- (iii) any *Bacillus* protein coding sequence
- (iv) any *Bacillus thuringiensis* protein coding sequence
- (v) any pesticidal or insecticidal protein coding sequence

- (vi) any insecticidal protein coding sequence from *Bacillus*
- (vii) any insecticidal protein coding sequence from *Bacillus thuringiensis*.

The application conveys that the inventors contemplated these variations when the application is read as a whole. (See Baum Declaration at paragraph 3.13.)

Finally, it is worth noting that species of *Bacillus* other than *B.t.* were known to have insecticidal properties by 1989, when the application was filed. (See Baum declaration at paragraph 3.14 and literature cited therein.)

For these reasons, the rejection of claims 47, 51, 55, 63, 112, 113, 117 and 118 was improper, and should be withdrawn.

B. Coding sequences devoid or substantially devoid of ATTTA sequences or polyadenylation signal sequences are described in the specification.

The Office contends that the method of claims 47, 51, 55, 59, 63, 67, 112, 113, 117, 119, 120, 122, 124, 126, and 128 is not supported by the specification because the disclosure allegedly does not describe coding sequences devoid or substantially devoid of ATTTA sequences but not devoid or substantially devoid of polyadenylation signal sequences, and *vice versa*. (Office Action, page 6, paragraph 8, part (b).)

As a preliminary matter, it appears that the Office did not identify a proper claim set in the rejection. While some of the claims (e.g., claims 63, 67, 112, 117, 126, and 128) use the phrases in question, others do not. For example, most of the other rejected claims specify “reducing” the number of occurrences of ATTTA or polyadenylation signal sequences, or making a gene with fewer of them than the starting sequence. If a claim does not use the allegedly offending language, the rejection should be withdrawn.

Second, it is clear that the application describes variations of the method of the invention where substantially all of a single type of problem sequence (ATTAA or polyadenylation signal) are targeted, *without the necessity* of also targeting substantially all of the other type of problem sequence. (See Baum Declaration at paragraphs 4.2-4.5.)

The application teaches at pages 22-23 that “In its most rigorous application, the method of the present invention involves the modification of an existing structural coding sequence (“structural gene”) which codes for a particular protein by removal of ATTTA sequences and putative polyadenylation signals by site directed mutagenesis of the DNA

comprising the structural gene. *It is most preferred that substantially all the polyadenylation signals and ATTAA sequences are removed although enhanced expression levels are observed with only partial removal of either of the above identified sequences.*" (Emphasis in underling and italic added.)

As explained in detail by Dr. Baum at paragraphs 4.2-4.5 of his declaration, this short excerpt from the application conveys a lot of information to the reader. First, the underlined, non-italicized portion conveys that the inventors considered removal of both ATTAA and polyadenylation signal sequences to be a highly effective variation of the invention – the most rigorous application of the invention.

The italicized, non-underlined excerpt further explains that it is *most preferred* that substantially all of both types of sequences be removed. It would be quite clear to a reader that removing substantially all of a sequence would result in a modified sequence that was substantially devoid – or in the extreme case completely devoid – of the sequence in question. (See Baum Declaration at paragraph 4.3.)

In the excerpt that is underlined and italicized, the specification explains that the invention can be practiced by removing either type of problem sequence, including removal of only some (not all or substantially all) of one type of problem sequence. In the context of the paragraph, the phrase "only partial removal" would have been understood to mean removal of some, but not necessarily all, of the occurrences of a type of sequence. The phrase "of either of the above identified sequences" would have been understood in the context of the paragraph to mean either the ATTAA sequences, or the polyadenylation signal sequences, without the necessity of removing both types of problem sequences. (See Baum Declaration at paragraph 4.3.)

Thus, these short excerpts from the application literally convey that all of the following techniques would be effective for enhancing expression, and were all variations of the invention:

- (i) removal of some of the ATTAA's, without removing polyadenylation signal sequences;
- (ii) removal of some of the polyadenylation signal sequences, without removing any of the ATTAA's; and

- (iii) removal of substantially all of the ATTTA's, and removal of substantially all of the polyadenylation signal sequences.

However, as explained by Dr. Baum in paragraph 4.4 of his declaration, these three variations of the invention are merely three literal teachings of a few sentences in the application – the same sentences and the rest of the application convey other variations to the reader as well. For example, a reader would understand from these few sentences that the inventors were teaching that the more of either type of problem sequence that was removed, the better the expression would be. (See also page 29 of the application, which emphasizes minimizing problem sequences: “The resulting sequence should be examined to ensure that there are minimal putative plant polyadenylation signals and ATTTA sequences.”) In other words, without spelling it out in word-for-word detail, these sentences convey to the reader the following additional variations of the invention:

- (iv) removal of some of the ATTTA's, and removal of some of the polyadenylation signal sequences; the reader would have understood that this variation would be better than variation (i) or (ii) because it is closer to the most preferred embodiment – the inventors conveyed that “removing more” is better (more preferred);
- (v) removal of *all or substantially all* of the ATTTA's, without the necessity of removing polyadenylation signal sequences; the reader would have understood that this variation would be better than variation (i) because the inventors conveyed that “removing substantially all” is better (more preferred);
- (vi) removal of *all or substantially all* of the polyadenylation signal sequences, without the necessity of removing any of the ATTTA's; the reader would have understood that this variation would be better than variation (ii) because the inventors conveyed that “removing substantially all” is better; and
- (vii) removal of *all* of the ATTTA's *and all* of the polyadenylation signal sequences; the reader would have understood that this variation should be better than all of the other variations, because the inventors conveyed that “minimizing” either type of sequence is better, and removing both types of sequence is better than removing only one type of sequence.

(Baum Declaration at paragraph 4.4.)

The Examples also contribute to the teachings in the application that removing either type of problem sequence alone is sufficient, and the higher percentage of occurrences that are eliminated, the better that expression is expected to be in transformed plants. In the Examples section, the inventors summarized a large number of experiments where parts or all of insecticidal protein coding sequences were altered by eliminating problem sequences. Sometimes substantially all of one or both types of problem sequence (ATTAA or polyadenylation signal) were removed (see, e.g., Examples 2 and 3); sometimes all of occurrences of a problem sequence were removed (see, e.g., Examples 2 and 3). In at least one variation described in Example 1, using the “BTK240” primer, a construct was made in which only a few occurrences of one type of problem sequence (three polyadenylation signal sequences) were removed. Collectively, the examples also convey that the inventors contemplated all of the different variations of the invention enumerated above, and convey that better results can be expected when more occurrences of either (or preferably both) types of problem sequence are eliminated. (See Baum Declaration at paragraph 4.5.)

For all of these reasons, the specification satisfies the written description requirement, and the rejection under Section 112, first paragraph, should be withdrawn.

C. “Multiple starting sequences”

In paragraph 8, part (c) of the Action, the Patent Office rejected claims 55 and 67, alleging lack of adequate description “for the starting material being sequences encoding portions of any two or more insecticidal polypeptides, as in claims 55 and 67. The only multiple starting sequences originally conceived are specific *B.t.* insecticidal proteins.” (Action at p. 6.) The Patent Office rejected claims 59, 91-92, and 113-114 for related reasons. (*Id.* at p. 7.)

Applicants traverse the rejection insofar as the Patent Office is asserting that the only multiple starting sequences originally conceived are “specific” *B.t.* insecticidal proteins. The Examples in the application would be understood to be representative, and not limiting, and a person skilled in the art would have concluded from reading the application that fusions of *B.t.* insecticidal proteins were contemplated, in a generic sense. Persons in the field would have known in 1989 that a number of *B.t.* insecticidal protein coding sequences had been characterized, and conservative regions had been identified, and toxicity had been localized to the C-terminus. The modular nature of *B.t.* insecticidal protein sequences used

for making a fusion according to Example 3 would have been understood to be representative of a variation of the invention contemplated by the inventors. (See Baum Declaration at paragraphs 5.2 and 5.3.)

The rejection is moot insofar as claims 55, 59, 67, and 114 have been amended to specify that the two or more insecticidal polypeptides are *B.t.* insecticidal proteins, and claim 113 has been amended to recite “a wildtype *Bacillus* coding sequence.” Claims 91-92 already recite “*B.t.*” The amendment of these claims to specify “*B.t.*” is solely to expedite allowance of claims directed to a preferred embodiment, and is not intended as an admission that other hybrids were not also contemplated. Nothing in the application can be construed as excluding hybrid constructs from the generic teachings of the application. The method is not dependent on the particular coding sequence used as starting material. (See Baum Declaration at paragraphs 5.2 and 5.3.)

D. Fusions with a chloroplast transit peptide or secretory signal sequence.

In paragraph 8, part (d), the Patent Office rejected claim 108, alleging inadequate support for using coding sequences for an amino-terminal chloroplast transit peptide or secretory signal sequence attached to “any” protein. (Action at p. 7.) The Patent Office only acknowledges support for attaching these peptides to *B.t.* crystal proteins. The Applicants respectfully traverse.

As explained in the previous section, the specification plainly explains that aspects of the invention that were described in the context of *B.t.* proteins were described that way for brevity. The reader would not have understood aspects described *in relation* to *B.t.* proteins to be limited to *B.t.* proteins, but rather, to be representative of other embodiments. (See Baum Declaration at paragraph 6.2.)

Moreover, the specification clearly describes use of the chloroplast transit peptide and secretory signal sequence modifications as being generally applicable to all protein coding sequences modified according to the invention. (See Baum Declaration at paragraph 6.3.) For example, the application states, “The DNA construct of the present invention also contains a modified or fully-synthetic structural coding sequence which has been changed to enhance the performance of the gene in plants. In a particular embodiment of the present invention the enhancement method has been applied to design modified and fully synthetic genes encoding the crystal toxin protein of *Bacillus thuringiensis*. The

structural genes of the present invention may optionally encode a fusion protein comprising an amino-terminal chloroplast transit peptide or secretory signal sequence (see for instance, Examples 10 and 11).” (Fischhoff application at pages 31-32.) Within this quotation, there is a clear contrast between the “particular embodiment” related to crystal toxin proteins of *B.t.*, in the second sentence, and the general teachings in the first and third sentences. The teachings about the chloroplast transit peptide and secretory signal sequence are general teachings pertaining to “the structural genes of the present invention” (which are described in both general and preferred embodiments).

In addition, the foregoing quote is found *before* the Examples section, in a section titled “Plant Gene Construction.” The title of this section is not about *B.t.* exclusively, but about any structural gene (encoding any plant or non-plant protein) modified according to the invention for improved expression in plants. The statement about optional inclusion of a chloroplast transit peptide or secretory signal, like the section heading, is general in nature. It expresses optional improvements for *any* modified coding sequence made according to the invention. In fact, the parenthetical use of “for instance” (when referring to Examples 10 and 11) combined with the general title “Plant Gene Construction” further confirms for the reader that the chloroplast transit peptide or secretory signal sequence is for any modified coding sequence, of which crystal proteins are only one category. (Baum Declaration at paragraph 6.4.)

E. Modified genes with no more than specified numbers of problem sequences.

In paragraph 8, part (e), the Patent Office rejected claims 71-76, alleging that the application provides inadequate description for making any *Bacillus*-derived structural gene containing “no more than one, seven or two ATTAA and/or Table II polyadenylation sequences or none at all as in claims 71-76.” (Action at p.7). The Patent Office acknowledges that specific examples exist for each of these claims, but asserts that these teachings are only described in the context of specific *B.t.* sequences.

As already explained above, a reader would understand that specific examples were intended to teach general concepts, and it is improper to read the application as

narrowly as the Patent Office asserts. However, the rejection is moot with respect to claims 71-72 and 74-76 because these claims have been canceled.

For reasons set forth above in Section III.B., a reader would find that claims which specify that the modified gene has no occurrences of a problem sequence (e.g., claims 73 and 77) are adequately described. As explained by Dr. Baum in detail (e.g., Baum Declaration at paragraphs 4.3 and 4.4), the guidance provided in the application regarding removal of problem sequences consistently teaches that fewer occurrences in the modified sequence is better, even though results can be achieved with only a few modifications. The application explicitly says that substantially all problem sequences are removed in the most preferred embodiments, and there are Examples where all of a problem sequence have been removed. (See, e.g., Example 3.) Based on these and related teachings, a person of ordinary skill would understand that the inventors contemplated removal of all occurrences of either type of problem sequence (ATTTA or polyadenylation signal sequence) or both types, as embodiments of the invention. (Baum Declaration at paragraphs 4.3-4.5.)

F. The rejection relating to claims that recite “62%” is moot.

The Patent Office rejected claims 79-80 and 136, alleging that the limitation 62% (A+T) is described only with reference to *B.t.* (Action at p. 7, paragraph 8(f).) The claims have been amended to recite *B.t.* or depend from claims that specify *B.t.*, or recite *B.t.* rendering the rejection moot.

G. The rejection of claim 128 is moot.

In paragraph 8(h), the Patent Office rejected claim 128, alleging that the original application failed to “provide support for the starting material being sequences encoding portions of any two or more polypeptides.” Claim 128 has been amended to read, “A method of making a structural gene that encodes a protein, the method comprising: combining coding sequences to form a structural gene that encodes a protein, wherein said coding sequences and the structural gene are devoid or substantially devoid of polyadenylation signal sequences listed in Table II.” The amended claim finds support throughout the application, which describes making hybrids of modified and wildtype sequences and also making a completely synthetic gene as one variation of the invention. (See, e.g., page 28: “It is evident to those skilled in the art that while the above description is directed toward the modification of the DNA sequences of wild-type genes, the present

method can be used to construct a completely synthetic gene for a given amino acid sequence. ... The resulting sequence should be examined to ensure that there are minimal putative plant polyadenylation signals and ATTTA sequences.”) Thus, the rejection of claim 128 is moot.

H. Conclusion as to Written Description

For the foregoing reasons, one of ordinary skill in the art would have understood Applicants to be in possession of the invention as presently claimed, so the rejections under 35 USC §112, first paragraph, should be withdrawn.

IV. The Rejections Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn.

The Patent Office rejected claims 47-112, 117, 118, and 120-141 under 35 U.S.C. §112, second paragraph, alleging failure to particularly point out and distinctly claim the invention. This rejection is traversed for the reasons set forth below.

A. The term "substantially devoid" is not indefinite as used in the claims.

The Office rejected claims 63-68, 112, 117-118, and 126-129, contending that “substantially devoid” is a relative term rendering these claims indefinite, because the specification assertedly does not disclose an upper limit on “substantially devoid.”

Recitation of “substantially” to modify a claim term does not render a claim indefinite when the recitation serves to reasonably describe the claimed invention to those of skill in the art. *Andrew Corp. v. Gabriel Elec., Inc.*, 847 F.2d 819, 821-22 (Fed. Cir. 1988) (“The criticized words are ubiquitous in patent claims.”). “Substantially devoid” need not have a fixed meaning (i.e., fixed upper limit) to satisfy Section 112, second paragraph. Compare *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002) (“Expressions such as ‘substantially’ are used in patent documents when warranted by the nature of the invention, in order to accommodate the minor variations that may be appropriate to secure the invention. Such usage may well satisfy the charge to ‘particularly point at and distinctly claim’ the invention 35 U.S.C. §112, and indeed may be necessary in order to provide the inventor with the benefit of his invention.”). “Substantially” is commonly used in

claims to avoid a strict numerical boundary to a specified parameter, i.e., “devoid,” without sacrificing definiteness. *Ecolab Inc., v. Envirochem, Inc.*, 264 F.3d 1358, 1367 (Fed. Cir. 2001). Indeed, the Federal Circuit recognized that “substantially” and similar expressions “accommodate the minor variations that may be appropriate to secure the invention.” *Id.*

Here, the plain meaning of “substantially” is that it modestly broadens the absolute nature of the term “devoid.” Thus, a coding sequence is “substantially devoid” of a problem sequence if the coding sequence contains only one or a few of the problem sequences. (See Baum Declaration at paragraph 8.3.) “Substantially devoid” reasonably describes the invention with precision appropriate to the technology and, therefore, satisfies the statutory requirement for definiteness as interpreted by the Federal Circuit. See *Verve*, 311 F.3d at 1120 (noting that phrases such as “substantially” can satisfy the requirements of Section 112, second paragraph, by particularly pointing out and distinctly claiming the invention).

Furthermore, the specification provides an indication of the scope of the term “substantially devoid.” (See Baum Declaration at paragraph 8.4.) For example, page 22, line 24, to page 23, line 13, of the specification teaches that while substantially all polyadenylation signals and ATTAA sequences are removed, enhanced expression levels are observed upon partial removal of polyadenylation signals and ATTAA sequences within a subject sequence. In addition, Example 2 describes an experiment in which a synthetic insecticidal fragment of *B.t.k.* HD-1 was made that was devoid of ATTAA sequences and substantially devoid of Table II polyadenylation signal sequences (in this instance, only one). Example 3 describes a construct devoid of ATTAA, and substantially devoid (reduced in this example from 18 to 2) of Table II polyadenylation signal sequences. The specification teaches that the purpose of removing polyadenylation signals and ATTAA sequences is to increase expression of a structural gene encoding a protein. The claims, taken in view of the specification, clearly delineate the metes and bounds of the claims such that one skilled in the art would understand what is claimed. See *Adv. Cardiovascular Sys., Inc., v. Scimed Life Sys.*, 96 F. Supp. 2d 1006, 1020 (N.D. Cal. 2000) (holding that use of term “substantially larger” to describe catheter dimensions was definite where the specification provided two figures depicting catheter dimensions and noted the purpose of having a “substantially larger” cross-sectional dimension compared to perpendicular dimension).

When interpreting “substantially devoid” the Patent Office continues to concern itself with *the level of reduction*. As explained above and by Dr. Baum at paragraph 8.5 of his declaration, the claim term “devoid” does not mean “reduced,” and so the term “substantially devoid” should not be confused with “substantially reduced.” Focusing exclusively on the number removed is not an appropriate way to evaluate whether a modified sequence is substantially devoid because “substantially devoid” means that few are present. If a wildtype gene sequence had only two or one occurrence of a problem sequence, then it would be substantially devoid from the start (without removing any occurrences). By the same token, removal of many occurrences of a problem sequence does not make the resulting sequence “substantially devoid,” if many problem sequences are still present. For example, removal of 50 occurrences of ATTTA from a starting sequence that had 100 ATTTA sequences would represent a significant numerical reduction, but no one would conclude that the modified sequence (which still contained 50 ATTTA) was substantially devoid of ATTTA. (See Baum Declaration at 8.5.)

For all of these reasons, the term “substantially devoid” does not render the claims indefinite, and the rejection under Section 112, second paragraph, should be withdrawn.

B. “Substituting sense codons for codons in the coding sequence” does not render the claims indefinite.

The Office contends that the clause “reducing the number of said ATTTA sequences or the number of said polyadenylation signal sequences in the coding sequence by substituting sense codons for codons in the coding sequence” renders claims 47, 51, 55, 120, and 122 indefinite. The Patent Office is concerned that substituting any sense codon for a codon in the coding sequence would not necessarily reduce the number of ATTTA or polyadenylation signals. The Office suggests that only specific sense codons would reduce ATTTA sequences or polyadenylation signals.

The Office’s analysis does not consider what one of ordinary skill in the art would understand to be the invention. A patent claim is definite under Section 112 if one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification. *Morton Int’l. Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993). The specification describes this aspect of the invention at, e.g., page 25, line 3,

through page 29, line 10, and in the Examples. For instance, Example 1 details how substitute sequences were selected to replace coding sequence codons, and Figure 2 compares the wild-type HD-1 sequence with that resulting from substitution with other sense codons.

As explained by Dr. Baum in his declaration, the genetic code contains sixty-four codons, of which 61 are sense codons – they code for an amino acid. Table I in the specification (pages 26-28) lists the sense codons. The other three codons code for no amino acid and are sometimes called “stop codons.” (Baum Declaration at paragraph 9.2.) Because sense codons code for an amino acid, a reader in the field would understand the claim phrase “substituting sense codons in the coding sequence” to mean that the codon that is being introduced (substituted) encodes an amino acid. This clause of the claims excludes substituting a stop codon into the coding sequence, which would have the effect of truncating the encoded amino acid sequence. (Baum Declaration at paragraph 9.2.)

The Patent Office was correct when it commented that the codons in the coding sequence would already be sense codons. Because the method is about “substituting” to reduce occurrence of certain problem sequences, a person in the field would understand that the method is substituting a sense codon that is different from the codon in the starting sequence. (Baum Declaration at paragraph 9.3.) The word “substituting” should be given its proper meaning when construing the claims.

The Patent Office also was correct that only substitution of specific sense codons would achieve the stated purpose of reducing the number of ATTAA or polyadenylation sequences. However, the fact that not all sense codons would necessarily achieve the stated purpose in the claim does not cast doubt on the meaning of the phrase “substituting sense codons in the coding sequence.” The claim simply is specifying two requirements – that the codon that is substituted into the coding sequence be a sense codon, and that the number of occurrences of the problem sequence be reduced as a result of substitutions that are made.¹ Because a person in the field would be able to determine which of the sense codons eliminate an ATTAA or polyadenylation sequence and which do not, there is no uncertainty in the meaning of a claim limitation such as “reducing the number of said ATTAA sequences or the number of said polyadenylation signal sequences in the coding

¹ The reader also understands from the application that it may be appropriate to substitute codons in a coding sequence to achieve other purposes, such as avoidance of five consecutive (A+T) nucleotides. Not all of the codon substitutions must have the effect of eliminating an ATTAA or polyadenylation signal sequence.

sequence by substituting sense codons for codons in the coding sequence....” (Baum Declaration at paragraph 9.4.)

C. The method claims do not omit essential steps.

Lastly, the Office contends that claims 47, 51, 55, 120, 122, and 124 are incomplete for failing to recite an essential step of the claimed method. The Patent Office said, “The omitted steps are: making the structural gene comprising a coding sequence that encodes the protein of step (a). As currently written there is no connection between the starting material of part (a) and the making step (c) except the substituted codons -- the rest of the codons of the coding sequence of step (a) are not necessarily involved in step (c).”

(Action at p. 11, paragraph 9(c).) The Applicants respectfully traverse.

The claims all contain an appropriate connection between the starting material of part (a) and the making step (c). For example, in claim 47, the starting material encodes an insecticidal polypeptide, and the encoded protein of step (c) also must be insecticidal. Other claims have similar connections.

Second, no additional step is essential to practice the method. While the application teaches that, in some variations of the invention, the starting material and the modified gene should encode the same protein (e.g., original claim 3), it is clear that the invention does not require this. The application itself contains examples. For example, the specification teaches that it may be beneficial to start a protein with “Met-Ala” (which may involve mutating the second codon of a protein). (See Baum Declaration at paragraph 10.2.) Original claims 1-2 did not require retaining the starting amino acid sequence.

By the time that the application was filed, scientists were able to make mutations to proteins that were not activity-destroying, and the invention would be expected to work in such circumstances. The method focuses on improving expression based on elimination of problem sequences within a coding sequence, and the expression should be improved irrespective of whether the amino sequence is unchanged. (See Baum Declaration at paragraph 10.2.)

D. Conclusion as to Definiteness

For the above reasons, the claims particularly point out and distinctly claim the invention, and the rejection under Section 112, second paragraph, should be withdrawn.

V. Conclusion

In view of the above amendment, Applicants believe the pending application is in condition for allowance. The Examiner is invited to contact the undersigned attorney by telephone if there are issues or questions that might be efficiently resolved in that manner.

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